Distributed Drug Discovery (D3): Computational and Synthetic Chemists Working Together to Educate Students and Discover Drug Leads for Neglected Diseases

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Goals of Distributed Drug Discovery (D3):

• To discover drug leads for neglected diseases (e.g. malaria, leishmaniasis, trypanosomiasis, tuberculosis, helminth related)

• To educate science students and future drug discovery researchers through participation in neglected disease drug lead research
Distributed Drug Discovery (D3): Seeking Drug Leads Through Multiple Small-Scale Educational Resources

**Stage One**

D3 Directed Basic Chemistry Research

Computational Enumeration

Large D3 virtual catalogs → Computational Analysis

- Distribute
- Combine

Proposed potential drug leads → Chemical Synthesis

- Distribute
- Combine

Molecules for screening → Biological Screening

- Distribute
- Combine

Molecules screened

Many Individual Students

**Stage Two**

**Stage Three**

**Stage Four**

*J. Comb. Chem. 2009, 11, 3-13, 14-33, 34-43*
NSF Proposal for “Transforming Undergraduate Education in Science” (TUES)

Recommended For Funding With Final Official Notification Pending
D3: Tight Integration of Computation and Synthesis

Global Open-Access D3 Virtual Catalogs

Disease specific computational analyses by independent experts

- Malaria target molecules
- Tuberculosis target molecules
- Leishmaniasis target molecules
- Trypanosomiasis target molecules
- Other neglected diseases?

Key aspect of D3: Strong probability that D3 virtual molecules have the resources and documented chemistry to be realistically made

Synthesize selected target molecules through D3 synthesis network
Key Enabling Resources for D3:

1. Neglected disease computational modules ("Teach-Discover-Treat" TDT Initiative)

2. Software facilitating cooperation (Collaborative Drug Discovery – "CDD")

3. Open-access virtual catalogs of molecules readily made with D3 educational resources
Distributed Drug Discovery (D3): Synthesis Stage

**Stage One**

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- Distribute
- Combine

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Proposed potential drug leads

Chemical Synthesis

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Molecules for screening

Biological Screening

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Chemistry Precedence: In Nature
Amino Acids are Key Biological Precursors

Peptides and proteins
\[ \text{Generic Amino Acids} \xrightarrow{\text{reaction}} \text{Peptide} \]

Representative biomolecules derived from amino acids
- Amino acid tyrosine
- Dopamine
- Norepinephrine
- Morphine
- Amino acid tryptophan
- 5-Hydroxytryptamine (Serotonin)
- Lysergic Acid diethylamine (LSD)

Biosynthesis of Penicillin G
\[ \text{Various carboxylic acids} \xrightarrow{\text{reaction}} \text{Amino acid L-Cysteine} \xrightarrow{\text{reaction}} \text{Amino acid D-Valine} \xrightarrow{\text{reaction}} \text{Penicillin G} \]
In Lab: Many Biomimetic Drugs are Amino Acid Derived

**Antibiotics:** Inhibitors of transpeptidase

Substrate in bacterial cell wall synthesis

\[ \text{~dAla-dAla} \]

Nature's Design (and chemists' modification)

\[ \text{Amoxicillin} \]

**Antihypertensives:** Inhibitors of Zn metalloprotease

\[ \text{Pyr-Lys-Trp-Ala-Pro} \]

(Natural inhibitor from snake venom)

\[ \text{Enalapril (Merck)} \]

Prodrug of Potent ACE Inhibitor

**AIDS treatment:** Inhibitors of HIV Aspartyl protease

Cleavage sequence in protein = \(-\text{Arg-Phe-Pro-Leu}\)

\[ \text{Saquinavir (Roche)} \]

First HIV Protease Inhibitor

**Antiepileptic:** Regulates voltage-gated sodium channels and collapsin mediator protein-2

\[ \text{Generic Peptide Core} \]

\[ \text{Lacosamide (Vimpat)} \]
Just One Intense Chemistry Slide: Specific Example of Powerful Chemistry to Natural Product-Like Amino Acid Based Biomimetics

Key intermediate 1 leading to multiple scaffolds 2-5, and multiple combinatorial possibilities at R₁ and R₂

1. Resin-Bound Phenylalanine
2. Phenethanolamine
3. Cysteine ethyl ester
4. 5-Methoxytryptamine
5. Dopamine

J. Am. Chem. Soc. 2007, 129, 7077-7088
First D3 Project: Enabling Student Synthesis Of New Acylated Unnatural Amino Acids

20,000 (100x100x2) Acylated unnatural amino acids

(Virtual library numbers from conservative choice of R groups and n stereoisomers)

1,200,000 (200x50x30x4) Diketopiperazines

160,000 (200x20x20x2) Benzodiazepines

32,000,000 (200x200x200x4) Lactam peptidomimetics

120,000 (3x200x100x2) \( \alpha \)-substituted proline homologs

20,000 (200x50x2) Hydantoins

Scott/O'Donnell chemistry

3,000 (200x10x2) 1,4-Benzodiazepine-2,5-diones

Virtual library numbers from conservative choice of R groups and n stereoisomers
Simple, Inexpensive Solid-Phase Bill-Board Equipment

Bill-Board 6-pack  Bill-Board Drain Tray  Collection Vial Rack

*J. Comb. Chem. 2009, 11, 14-33* describes use of equipment in student labs
First D3 Student Lab Established at IUPUI

First Lab Session - Alkylation

\[
\text{Ph-N-Ph} \overset{\text{R}^1-\text{X} \text{ (5 equiv) Base = BTPP}}{\longrightarrow} \text{Ph-N-Ph}
\]

Second Lab Session - Acylation

\[
\text{Ph-N-Ph} \overset{1) \text{H}_2\text{O}^+ \ 2) \text{Et}_3\text{N}}{\longrightarrow} \text{H}_2\text{N-Ph-N-Ph} \overset{\text{R}^2\text{CO}_2\text{H DI/OHOB}}{\longrightarrow} \text{R}^2\text{N-Ph-N-Ph} \overset{\text{TFA}}{\longrightarrow} \text{R}^2\text{CO}_2\text{H}
\]

Third Lab Session - Cleavage

\[
\text{Ph-N-Ph} \overset{\text{TFA}}{\longrightarrow} \text{R}^2\text{CO}_2\text{H}
\]

Fourth Lab Session: Purify A1 and A2 by column chromatography

Fifth Lab Session: Obtain NMR on A1 and interpret LC/MS analytical data for all samples

3 x 2 Combinatorial Bill-Board Layout
(3 Alkylation agents R\(^1\)-X and 2 acylating agents R\(^2\)CO\(_2\)H)

Two different acylating agents R\(^2\)-CO\(_2\)H across rows A and B

Six unique compounds I, (five new, with A1 as a control)

J. Comb. Chem. 2009, 11, 14-33

Scale = 50 µmol
3.5 mL capacity fritted reaction vessels

= Polystyrene Wang resin bead
Adding Reagents

Lab with 36 Bill-Boards

216 Simultaneous Rxns

Success!
At the end of this experiment students learned:

- 4-step Solid-Phase Organic Synthesis
- Combinatorial chemistry, 6 reactions at a time
- μScale/milligram level (50 μmol/reaction) synthesis
- Silica gel chromatographic purification
- Gathering and interpreting NMR data
- Liquid chromatography/mass spectra interpretation

Students also connected to the “Real World” by:

- Learning about drug discovery research process
- Synthesizing and isolating novel potential drug leads
- Submitting compounds to NIH for screening
- Participating in Global student research
Distributed Synthesis: D3 Lab I Successfully Carried Out by Students at Five Global Locations

• Indiana University-Purdue University Indianapolis (IUPUI) (USA)

• University of Barcelona (Spain)

• Moscow State University (Russia)

• Medical University, Lublin (Poland)

• University of Indianapolis (USA)
Examples of D3 Laboratories Now In Operation

D3 Lab I: The combinatorial synthesis of acylated unnatural amino acids

Two variables - $R^1$ and $R^2$ - in synthetic recipe to create racemic 1: 100 different ingredients at each variable step will give rise to $> 20,000$ different compounds in virtual catalog.

D3 Lab IV: The combinatorial synthesis of acylated unnatural amino acid amides

Three variables - $R^1$, $R^2$ and $R^3$ - in synthetic recipe to create racemic 4: 100 different ingredients at each variable step will give rise to $> 2$ million different compounds in virtual catalog.
Distributed Drug Discovery (D3): Computational Stage

Stage One

D3 Directed Basic Chemistry Research

Computational Analysis

Large D3 virtual catalogs

Proposed potential drug leads

Many Individual Students

Chemical Synthesis

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Combine

Molecules for screening

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J. Comb. Chem. 2009, 11, 3-13
Converting D3 Enabled Chemistry Into D3 Virtual Catalogs for Computational Analysis

D3 Directed Basic Chemistry Research

Student development of D3 synthesis labs

D3 Enabled Synthetic Chemistry

Computational enumeration

Large D3 virtual catalogs

Proposed potential drug leads

Many Individual Students

Computational Analysis

Distribute

Combine
Computational challenge: Intuitive, open-access, reaction-based enumeration module
Generating (“Enumerating”) a 24,000+ D3 Virtual Catalog Based on Synthetic Sequence Enabled by D3 Lab I

Scaffold 1

R\(^1\) from R\(^1\)X (or side chain on naturally occurring amino acids)

R\(^2\) from 100 carboxylic acids

For free access: [https://www.collaborativedrug.com/register/iupui_d3](https://www.collaborativedrug.com/register/iupui_d3)

This site is maintained by Collaborative Drug Discovery (CDD)

*J. Comb. Chem. 2009, 11, 14-33, 34-43*
Examples from >24,000 Compound D3 Virtual Catalog

\( \text{J. Comb. Chem. 2009, 11, 14-33} \)
Challenge: Intuitive, open-access and educational computational modules for picking neglected disease drug-lead candidates from D3 virtual catalogs

↓

“Teach-Discover-Treat” (TDT) initiative
Proposed Integration of D3 Computation and Synthesis

Global Open-Access D3 Virtual Catalogs

Tuberculosis specific "Teach-Discover-Treat" module for computational analyses

Malaria target molecules

150 Target anti-tuberculosis molecules

Leishmaniasis target molecules

Trypanosomiasis target molecules

Other Neglected Diseases?

Schools A&B 10 target molecules

Schools C&D 25 target molecules

Schools E&F 25 target molecules

Schools G&H 40 target molecules

Schools I&J 50 target molecules

Replicated distributed synthesis

150 Target anti-tuberculosis molecules

Target molecules synthesized through D3 network
Distributed Drug Discovery (D3): Screening Stage

Stage One

- D3 Directed Basic Chemistry Research
- Computational Analysis
- Chemical Synthesis
- Biological Screening

Stage Two

- Large D3 virtual catalogs
- Proposed potential drug leads
- Many Individual Students

Stage Three

- Many Individual Students
- Molecules for screening

Stage Four

- Many Individual Students
- Molecules screened

J. Comb. Chem. 2009, 11, 3-13
**Key Strengths of D3 Project**

- Focus on neglected disease targets
- Open-access virtual catalogs of D3 accessible molecules for computational analysis/selection
- Inexpensive protocols to make selected molecules via multiple small-scale educational resources
- Coupled drug-lead discovery and education of future drug discovery researchers
- Simple, reproducible process for scale-up and analog production
Publications in First 2009 Issue of Journal of Combinatorial Chemistry
(Undergraduate co-authors in red, International collaborators in blue)

Editorial about the Distributed Drug Discovery Program:


Distributed Drug Discovery, Part 1: Linking Academia and Combinatorial Chemistry to Find Drug Leads for Developing World Diseases


Distributed Drug Discovery, Part 2: Global Rehearsal of Alkylating Agents for the Synthesis of Resin-Bound Unnatural Amino Acids and Virtual D³ Catalog Construction


Distributed Drug Discovery, Part 3: Using D³ Methodology to Synthesize Analogs of an Anti-Melanoma Compound

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>1,400 C344 students

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